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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/820,416	03/29/2001	David Bar-Or	4172-15-1	5597

22442 7590 06/23/2004

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EXAMINER

SHAHNAN SHAH, KHATOL S

ART UNIT

PAPER NUMBER

1645

DATE MAILED: 06/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>
	09/820,416	BAR-OR ET AL.
	Examiner Khatol S Shahnan-Shah	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 11 March 2004.
- 2a) This action is **FINAL**.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 48-68 is/are pending in the application.
- 4a) Of the above claim(s) 54,55,59,62 and 65 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 48-53,56-58,60,61,63,64 and 66-68 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All    b) Some \* c) None of:
1. Certified copies of the priority documents have been received.
  2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 3/11/04.
- 4) Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: \_\_\_\_\_.

**DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants have not submitted any new amendments or arguments.

2. Claims 48-68 are pending.

***Restriction Requirement***

3. Applicants comments in regard to claim 55 reading on the elected species cobalt, is noted.

Claim 55 refers to other ions on Groups 1b-7b or 8 of the Periodic Table of the elements not only cobalt.

4. Claims 48-53, 56-58, 60, 61, 63, 64 and 66-68 are under consideration. Claims 54-55, 59,62 and 65 are withdrawn from consideration as being drawn to non-elected inventions.

***Prior Citations of Title 35 Sections***

5. The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior office action.

***Prior Citations of References***

6. The references cited or used as prior art in support of one or more rejections in the instant office action have been previously cited and made of record. No form PTO-892 has been submitted with this office action.

***Information Disclosure Statement***

7. Applicants' Information Disclosure Statement, received, 3/11/2004 is acknowledged. The references

have been considered by the examiner, see attached 1449 forms.

***Rejections Maintained***

8. Rejection of claims 48, 49, 50-53, 56-58, 60-61, 63-64 and 66- 68 under 35 103 (a) made in paragraph 9 of the office action mailed July 02, 2002, paper # 13 is maintained.

The rejection was as stated below:

Claims 48, 49, 50-53, 56-58, 60-61, 63-64 and 66- 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bar-Or et al. (US Patent No: 5,227,307) in view of Crapo et al. (US Patent No. 5,994,339) and further in view of Young et al. (6,375,930).

Claims are drawn to a method of monitoring or assessing treatment of a disease or condition with a compound that produces free radicals comprising:  
a) obtaining a biological sample;  
b) treating the patient with a compound;

c) obtaining additional biological samples after treatment; and determining the change of albumin in the sample by:

- d) contacting each of the biological sample with excess quantity of a metal ion salt;  
e) determining the amount of bound metal ion to the albumin;  
f) determining if there is a change in the amount of bound metal ion.

Bar-Or et al. (US Patent No: 5,227,307) teach a method of monitoring disease or condition in a patient that produces free radicals comprising:

a) obtaining a biological sample and determining the change of albumin in the sample by:

b) contacting each of the biological samples with excess quantity of a metal ion

salt;

c) determining the amount of bound metal ion to the albumin;

d) determining if there is a change in the amount of bound metal ion.

(see abstract and claims).

Bar-Or et al. teach a method for detecting ischemic states (lack of oxygen) in a patient by contacting a sample of serum with a metal ion capable of binding to metal binding sites in the sample to form a mixture and then detecting the presence of unbound metal ion to determine the ischemic event (see example 1 and claims). Furthermore, the prior art teaches that several methods could be used to measure the metal ion binding to the albumin such as atomic absorption, atomic emission spectroscopy and determining the color intensity by spectrophotometer (see column 3, lines 44-54). Bar-Or et al. teach a variety of metal ion salts including cobalt (see column 5, lines 23-40). Bar-Or et al. teach that the quantity of free metal ions in the sample may also be detected by colorimetric means and teach a variety of color forming compounds (see column 6, lines 20-65). Bar-Or et al. (US Patent No: 5,290,519) teach a method of quantifying modified albumin, column 3, lines 14-22 recite that “ In the present method, a sample of serum, plasma, fluid or tissue from a patient is reached with metal ions, generally in the form of an aqueous salt solution, so that the metal ion become bound to the metal binding sites on the protein in the sample. Metal ions bind to the proteins containing metal ion- binding sites such as thiol, hydroxy, carboxy, amino groups present on the amino acids which constitute the protein.” Therefore, Bar-Or et al. teach modified protein (i.e. modified albumin) since metal binding capacity is reduced or inhibited in the albumin. Bar-Or et al. do

not teach treating patient with a compound or superoxide dismutase as a free radical scavenger. However, Crapo et al. teach treating patient with an effective amount of a mimetic of superoxide dismutase as a free radical scavenger (see column 1, background, column 2, summary of invention and claims specially claim 1). Crapo et al. do not teach photosensitizing agents and porfimer sodium. However, Young et al. teach photodynamic therapy and porfimer sodium (see column 3, lines 10-20 and column 4, lines 50-56). It would have *prima facie* obvious to a person of ordinary skill in art at the time the invention was made to use and combine the methods set forth in Bar-Or et al., Crapo et al. and Young et al. to obtain the claimed invention. One of ordinary skill in art would have been motivated with the reasonable expectation of success to develop a method of monitoring or assessing treatment of a disease by detecting or quantifying free radical damage as taught by Bar-Or et al. absent any convincing evidence to the contrary.

Applicants argue that Bar-Or et al. is directed to the diagnosis of one special condition – ischemia. Bar-Or et al. do not teach or suggest monitoring or assessing the effectiveness of treatment of patients with drugs that produce or reduce free radicals. Applicants further argue that the language of lines 23-25 of column 2 of Bar-Or et al. is referred to rehabilitative treatments for ischemia, such as angioplasty and the statement can not be interpreted to mean any other kind of treatment. Applicants further argue that this general language does not provide any motivation to combine the teachings of Bar-Or et al. and Crapo et al. and Young et al. and the examiner has improperly reconstructed the invention through hindsight.

Applicants' arguments filed 9/9/ 2003 have been fully considered but they are not persuasive.

It is the examiner's position that Bar-Or et al. teach or suggest monitoring or assessing the effectiveness of treatment of patients for example in column 2, lines 23-25 Bar-Or et al. recite "A further object of the invention is to provide a method for evaluating rehabilitated patients suffering from ischemia (myocardial infarction) to determine circulatory effectiveness", in column 9 lines 34-41 Bar-Or et al. recite "The results indicate that the present method can be used to detect ischemic states. The present method is effective in distinguishing between ischemic cardiogenic chest pain and non-cardiogenic chest pain. Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced other than as specifically described herein".

It is also the examiner's position that claims are drawn to a method of monitoring or assessing treatment of a disease or condition that produces free radicals. Ischemia is a disease or condition, which is frequently caused by arterial vessel disease. One feature of arterial vessel disease is the progression from the atherosomatous state to the sclerotic state in which large quantities of calcium enter the arterial musculature. The intracellular calcium activates the protease calpain, which converts xanthine dehydrogenase to xanthine oxidase. Xanthine oxidase acts on xanthine and hypoxanthine to form free radical (see Bar-Or et al. column lines 40-51). The instant specification in the paragraph bridging pages 12 and 13 recites, "The methods of the invention can be used to monitor and assess disease and conditions in which free radicals play a role." The paragraph further recites ischemia as one of these conditions (see page 13, line 4). Therefore, the invention is obvious over Bar-Or et al. in view of Crapo et al. and further in view of Young et al. In response to applicants' argument that the examiner's conclusion of

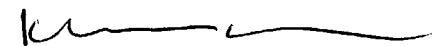
obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

***Conclusion***

9. No claims are allowed.
10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol S Shahnan-Shah whose telephone number is (571)-272-0863. The examiner can normally be reached on 7:30am-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette F Smith can be reached on (571)-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

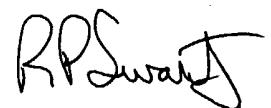


Khatol Shahnan-Shah, BS, Pharm, MS

Biotechnology Patent Examiner

Art Unit 1645

June 21, 2004



RPSwartz

RODNEY P SWARTZ, PH.D  
PRIMARY EXAMINER